REMARKS/ARGUMENTS

Claims 70-91 are pending. Claim 70 has been revised to refer to a method for detecting an environmental contaminant or toxin. Support for this limitation if found on page 1, lines 22-24 and page 2 and page 71, line 13. Claims 89 and 91 find support on page 9, line 13 of the specification. Claim 90 tracks the language of Claim 70 and finds support also on page 2, lines 19-21. Accordingly, the Applicants do not believe that any new matter has been added.

The Applicants thank Examiner Forman for the courteous and helpful interview on October 25, 2005. The *in vitro* method of Nilsson for evaluating the antagonistic vs. agonistic effects of a test substance was reviewed. The Examiner indicated that this method disclosed the various comparative steps of the present method. For example, it was suggested that the various controls in col. 5, lines 47-54, tracked (A), (B) and (C) in Claim 70 with tamoxifen being the endocrine disrupting substance and estradiol being the endocrine hormone; and that the table at the top of col. 6 compares protein expression with no hormone added, just estradiol, just tamoxifen and the combination of estradiol and tamoxifen. Therefore, the Examiner indicated that these steps were analogous to those of the present method. The Examiner also indicated that while Nilsson does not disclose an RNA-based method, that such a method is well-known as disclosed by Falb. To attempt to avoid this rejection, it was suggested that the claims be directed to a particular application disclosed by the specification, but not by the prior art, for example, to detection of an environmental contaminant or toxin. The claims have now been so amended. Favorable consideration and allowance of this application is now respectfully requested.

Request to Withdraw Final Rejection

The Applicants traverse the finality of the last Official Action. This action should not have been made final since the Applicants significantly revised the claims and the new limitations were not previously examined. For example, Claim 76 requires detecting one or more unique bands and independent Claim 70 requires a unique gene expression. The Official Action assumes that the term "unique gene expression" encompasses the same scope as the previously examined claims. Under this assumption a relative 10% decrease of expressed RNA or protein compared to a control value would be regarded as a "unique" gene expression. The Applicants submit that the word "unique" has been misconstrued to have the same meaning as the word "different", but that it should properly be construed as an absolute term requiring the expression of a unique gene product in one pattern, but not in another. This absolute definition of "unique" is consistent with the common definition of this word. According to the American Heritage Dictionary (excerpt attached):

> For many grammarians, **unique** is the **paradigmatic absolute term**, a shibboleth that distinguishes between those who understand that such a term cannot be modified by an adverb of degree or a comparative adverb and those who do not (emphasis added).

Thus, the word unique should not have been construed as a relative term, but as an absolute term requiring the gene expression to occur in one sample, but not in another. Therefore, the scope of the new claims is different that than of the previously presented claims and the last Official Action should not have been made FINAL. Moreover, had the sense of the word "unique" been unclear, an indefiniteness rejection should have been imposed and such an indefiniteness rejection would also have precluded the imposition of a final rejection. Accordingly, the Applicants respectfully request that the Examiner withdraw the finality of the last Official Action.

Rejection—35 U.S.C. 102

Claims 70, 73, 81-84, and 86-88 were rejected under 35 U.S.C. 102(b) as being anticipated by Nilsson et al., U.S. Patent No. 5,578,445. This rejection is moot in view of the revision of independent Claim 70. Nilsson et al. do not disclose a method of detecting endocrine disruption based on the unique expression of a gene expression product in "expression pattern (1)" (the sample containing both the hormone and the endocrine disrupting compound), nor do they disclose a method for detecting an environmental toxin or contaminant. Moreover, Nilsson is directed to a method involving estrogens and thus cannot anticipate Claims 90-91; nor are Claims 89 and 91 anticipated, because Nilsson does not disclose or suggest test samples having one ppb or one ppt of an environmental contaminant or toxin.

Rejection—35 U.S.C. 103

Claims 71-72, 74-76, 80 and 85 were rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al., U.S. Patent No. 5,578,445, in view of Falb, U.S. Patent No. 5,849,578. Nilsson et al. do not make obvious the present invention, because they do not provide a reasonable expectation of success for the highly sensitive method of the present claims. There is no recognition in Nilsson et al. that by detecting endocrine disruption in the presence of the endogenous hormone that a better and more sensitive process is obtained. On the other hand the two Declarations previously submitted by the Applicants show that specifically comparing the gene expression in the presence of the combination of the endocrine hormone and the disrupting substance, provides a superior method to a conventional method which does not include this combination.

This superior sensitivity is shown in the Declaration of Mitsuko Ishihara filed August 12, 2003. This Declaration shows that a unique band in sample (A) only in which cells were exposed to 30nM T3 (thyroid hormone) and 1nM TCDD (dioxin), but not in control cells exposed to only 30nM T3 or only 1nM TCDD (dioxin). This result shows the previously unrecognized superior sensitivity of the claimed method for detecting endocrine disruption even when the endocrine disrupting substance is present in a very low concentration.

The Declaration filed August 12, 2002 also shows the previously unrecognized superior sensitivity of the present method. A conventional method where the endogenous hormone is not added to the test sample was compared to the claimed method where the test substance is detected in the presence of an endogenous hormone. As shown in Table 3, the claimed method efficiently detects numerous genes not detected by the conventional method. However, the cited prior art, Nilsson et al. do not provide a reasonable expectation of success for such a method. There is no suggestion in the prior art that the inclusion of the endogenous hormone along with the test sample provide any benefit at all, nor any reasonable expectation of the improved sensitivity of the claimed method.

Moreover, Nilsson do not disclose or suggest the elements of the invention discussed above, such as a method for detecting an environmental contaminant or toxin. The object of Nilsson is to screen drug candidates that merely have a relative antagonistic or agonistic effect, that is, an effect of a test compound on increasing or decreasing biological responses mediated via particular hormone receptors (abstract, and col. 1, lines 34-36). Thus, the Nilsson examples only describe the detection of a known protein produced in response to activation of a hormone receptor. For example, Nilsson exemplifies measuring the expression of the pS2 antigen (col. 5, lines 25-*et seq.*), cathepsin D protein (col. 8, line 34-*et seq.*) or alkaline phosphatase protein (col. 13, line 36-*et seq.*). It is not possible to detect an endocrine disrupting substance as in the present invention which causes a gene expression

entirely different from a gene expression that is induced only by the effect of a particular hormone.

One the other hand, the present invention is directed to a method of detecting an environmental contaminant or toxin by determining the ability of the contaminant or toxin to cause the expression of a unique gene product in expression pattern (1).

Moreover, Nilsson is directed to a method involving estrogens and thus does not disclose or suggest the method of Claims 90-91 and does not disclose or suggest test samples having one ppb or one ppt as required by Claims 89 and 91.

Therefore, the Applicants respectfully submit that this rejection would not apply to the present claims.

Rejection—35 U.S.C. 103

Claims 77-79 were rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al., U.S. Patent No. 5,578,445, in view of Falb, U.S. Patent No. 5,849,578 and further in view of Horwitz et al., U.S. Patent 6,750,015.

Nilsson and Falb have been addressed above and do not disclose or suggest or provide a reasonable expectation of success for a method of detecting an environmental contaminant or toxin which is an endocrine disrupting substance which acts in combination with an endocrine hormone to produce disruption. Horwitz et al. which was cited for its teaching of SDS-PAGE, but does not otherwise remedy the deficiencies of the other two references. Accordingly, the Applicants respectfully request that this rejection also be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is currently in condition for allowance. Early notice to that effect is earnestly requested.

Respectfully submitted,

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The American Heritage® Dictionary of the English Language: Fourth Edition. 2000.

unique

SYLLABICATION: u·nique

PRONUNCIATION: yo͞o-nēk'

ADJECTIVE: **1.** Being the only one of its kind: *the unique existing example of Donne's handwriting.* **2.** Without an equal or equivalent; unparalleled. **3a.** Characteristic of a particular category, condition, or locality: *a problem unique to coastal areas.* **b.** *Informal* Unusual; extraordinary: *spoke with a unique accent.*

ETYMOLOGY: French, from Old French, from Latin ūnicus. See **oi-no-** in Appendix I.

OTHER FORMS: **u·nique'ly** —ADVERB
u·nique'ness —NOUN

USAGE NOTE: For many grammarians, *unique* is the paradigmatic absolute term, a shibboleth that distinguishes between those who understand that such a term cannot be modified by an adverb of degree or a comparative adverb and those who do not. These grammarians would say that a thing is either unique or not unique and that it is therefore incorrect to say that something is *very unique* or *more unique* than something else. Most of the Usage Panel supports this traditional view. Eighty percent disapprove of the sentence *Her designs are quite unique in today's fashions.* But as the language of advertising in particular attests, *unique* is widely used as a synonym for *worthy of being considered in a class by itself, extraordinary* and if so construed it may arguably be modified. In fact, *unique* appears as a modified adjective in the work of many reputable writers. A travel writer states that *"Chicago is no less unique an American city than New York or San Francisco,"* for example, and the critic Fredric Jameson writes *"The great modern writers have all been defined by the invention or production of rather unique styles."*

Although these examples of the qualification of *unique* are defensible, writers should be aware that such constructions are liable to incur the censure of some readers. See Usage Notes at **absolute, equal, infinite**.

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